



## Article

# Interventions for treating anxiety after stroke

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<http://dx.doi.org/10.1002/14651858.CD008860.pub2>

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# Interventions for treating anxiety after stroke (Review)

Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE, Watkins CL, Knapp P



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[Intervention Review]

## Interventions for treating anxiety after stroke

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**Editorial group:** Cochrane Stroke Group.

**Publication status and date:** New, published in Issue 12, 2011.

**Review content assessed as up-to-date:** 6 May 2011.

**Citation:** Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE, Watkins CL, Knapp P. Interventions for treating anxiety after stroke. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No.: CD008860. DOI: 10.1002/14651858.CD008860.pub2.

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### ABSTRACT

#### Background

Approximately 20% of stroke patients experience anxiety at some point after stroke.

#### Objectives

To determine if any treatment for anxiety after stroke decreases the proportion of patients with anxiety disorders or symptoms, and to determine the effect of treatment on quality of life, disability, depression, social participation, risk of death or caregiver burden.

#### Search methods

We searched the trials register of the Cochrane Stroke Group (October 2010), CENTRAL (*The Cochrane Library* 2010, Issue 4), MEDLINE (1950 to October 2010), EMBASE (1947 to October 2010), PsycINFO (1806 to October 2010), Allied and Complementary Medicine database (AMED) (1985 to October 2010), Cumulative Index to Nursing and Allied Health (CINAHL) (1982 to October 2010), Proquest Digital Dissertations (1861 to October 2010), and Psychological Database for Brain Impairment Treatment Efficacy (PsycBITE) (2004 to October 2010). In an effort to identify further published, unpublished and ongoing trials, we searched trial registries and major international stroke conference proceedings, scanned reference lists, and contacted select individuals known to the review team who are actively involved in psychological aspects of stroke research, and the Association of the British Pharmaceutical Industry.

#### Selection criteria

Two review authors independently screened and selected titles and abstracts for inclusion in the review. Randomised trials of any intervention in patients with stroke where the treatment of anxiety was an outcome were eligible.

#### Data collection and analysis

Two review authors independently extracted data for analysis. We performed a narrative review. A meta-analysis was planned but not carried out as studies were not of sufficient quality to warrant doing so.

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**Interventions for treating anxiety after stroke (Review)**

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## Main results

We included two trials (three interventions) involving 175 participants with co-morbid anxiety and depression in the review. Both trials used the Hamilton Anxiety Scale (HAM-A) to assess anxiety, and neither included a placebo control group. One trial randomised 81 patients to paroxetine, paroxetine plus psychotherapy or standard care. Mean level of anxiety severity scores were 58% and 71% lower in the paroxetine, and paroxetine plus psychotherapy groups respectively compared with those in standard care at follow-up ( $P < 0.01$ ). The second trial randomised 94 stroke patients, also with co-morbid anxiety and depression, to receive buspirone hydrochloride or standard care. At follow-up, the mean level of anxiety was significantly lower for those receiving buspirone relative to controls ( $P < 0.01$ ). Half of the participants receiving paroxetine experienced adverse events that included nausea, vomiting or dizziness; however, only 14% of those receiving buspirone experienced nausea or palpitations. No information was provided about the duration of symptoms associated with adverse events.

## Authors' conclusions

There is insufficient evidence to guide the treatment of anxiety after stroke. The data available suggest that pharmaceutical therapy (paroxetine and buspirone) may be effective in reducing anxiety symptoms in stroke patients with co-morbid anxiety and depression. No information was available for stroke patients with anxiety only. Randomised placebo controlled trials are needed.

## PLAIN LANGUAGE SUMMARY

### Interventions for treating anxiety after stroke

Anxiety after stroke occurs frequently and can be treated with antidepressants, other anxiety reducing drugs, or psychological therapy. This review of two trials, which included 175 participants, found that antidepressant and anxiety reducing drugs decreased the severity of anxiety symptoms. However, they also increased side effects. One trial showed that combining an antidepressant with psychotherapy also decreased anxiety symptom severity but not to a greater extent than antidepressant treatment alone. The findings are only applicable to stroke patients with both anxiety and depression as we did not find any studies that considered stroke patients with anxiety only. Future research will need to ensure that stroke patients with anxiety alone are also included in trials, and these trials should include a placebo control group.

## BACKGROUND

### Description of the condition

Stroke and anxiety disorders are both major public health problems. While stroke is the leading cause of adult disability (Department of Health 2007), anxiety is the most common mental health disorder (Lepine 2002). Prevalence of anxiety after stroke ranges between 20% to 25% (Burvill 1995; Lincoln 1998), and it remains a common problem several years after the stroke event (Sharpe 1990; Astrom 1996; Langhorne 2000).

There are several distinct types of anxiety disorders such as general anxiety disorder (GAD), panic disorder, social phobia, obsessive compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). While categorically different, they share similar hallmark characteristics of excessive and irrational fear, subjective apprehension, and difficulty and distress in managing daily tasks (Gelder

2006). Furthermore, although diagnosed with an anxiety disorder, many individuals experience significant levels of physical (e.g. heart palpitations, shortness of breath), cognitive (e.g. feeling of losing control), or behavioural (e.g. avoidance of certain stimuli) symptoms of anxiety that can affect their daily lives. All types of anxiety disorders have been observed in stroke patients (House 1991; Max 2002), and have been shown to have a negative impact on quality of life (Ahlsio 1984). Co-morbidity with depression is also very high (Castillo 1993). Studies found that depression is more severe and longer lasting in those with co-morbid anxiety (Shimoda 1998), and stroke patients with co-morbid anxiety and depression had higher levels of impairment in activities of daily living, more cognitive impairment and fewer social ties than those with depression alone (Shimoda 1998).

Differentiating between normal worries and the emergence of pathological anxiety disorders, or clinically significant levels of anxiety symptoms, is difficult for several reasons. Being of advanced

age or having limited verbal ability increases the difficulty in identifying persons suffering from anxiety (Van Rijswijk 2009), both of which are common within the stroke population. Other practical problems, such as difficulty in accessing specialist mental health services, patients not presenting for treatment, and lack of clinical guidelines specific to stroke patients with anxiety problems, mean that individuals may go untreated.

## Description of the intervention

We were interested in pharmaceutical, psychological, or any alternative therapy whose primary purpose was to treat anxiety disorders or significant levels of anxiety symptoms in stroke patients. Given the potential diversity of anxiety states, we did not limit our criteria to an a priori list of therapies. We did, however, expect to find studies that treated anxiety according to evidence-based guidelines, such as those recommended by the National Institute for Health and Clinical Excellence (NICE 2011), which outline pharmaceutical and psychological interventions used to treat certain anxiety disorders in the general population. To our knowledge no specific guidelines have been developed for the treatment of anxiety in stroke patients.

## Pharmaceutical therapies

Several classes of drugs can be used to treat anxiety disorders. The drugs vary according to the neurotransmitters which they are purported to affect.

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressant drugs used to treat anxiety. Serotonin is a neurotransmitter involved in regulating mood. SSRIs, such as fluoxetine, sertraline, escitalopram, paroxetine and citalopram, are commonly prescribed for panic disorder, OCD, PTSD and social phobia (NIMH 2009). Pharmacologically, SSRIs inhibit the post-release reuptake of serotonin by pre-synaptic nerve terminals, hence increasing the level of available serotonin in the brain (Craig 2003).

Tricyclic antidepressants (TCAs) (e.g. imipramine) are an older generation of antidepressant drug developed in the 1950s, and have been replaced for the most part by SSRIs. They are, however, still recommended in clinical guidelines for treating GAD and panic disorder (NICE 2011). TCAs act as serotonin and norepinephrine reuptake inhibitors, which results in increasing the extracellular concentration of these neurotransmitters hence enhancing neurotransmission.

Benzodiazepines (e.g. diazepam and alprazolam) are anxiolytics used to treat GAD and social phobia (Baldwin 2005), and in some instances specific phobia (NICE 2011). These drugs enhance the effect of the gamma-aminobutyric acid (GABA) neurotransmitter which serves to reduce the somatic symptoms associated with anxiety, such as muscle tension and insomnia but are only recommended for short-term use.

Zopiclone, zaleplone, and zaleplon (Z-drugs), are hypnotics that can be prescribed to assist for sleep disturbance seen in GAD and PTSD (NICE 2005). These drugs behave in a similar way to benzodiazepines except they have a shorter half-life.

## Psychological therapies

Various forms of psychological therapies are available for treating anxiety. They may be welcomed by individuals (especially older people) who may prefer not to use psychotropic drugs (Givens 2006). This preference is based on concern about dependence, prior negative experiences and the fact that many individuals do not view their psychological symptoms as a medical illness (Givens 2006). Several forms of psychological therapies are described below.

Behaviour therapy is based on learning theory, and patients are shown approaches to develop adaptive ways of behaving. The aim of behaviour therapy is to treat anxiety through techniques designed to reinforce desired behaviours and eliminate undesired ones.

Cognitive therapy is based on the cognitive model which hypothesises that a person's emotions and behaviours are influenced by their perception of events. Hence it is not the situation itself that determines how a person feels but rather the way in which they construe the situation (Beck 1979).

Cognitive behaviour therapy (CBT) incorporates elements from both cognitive and behaviour therapy. It seeks to change a person's thoughts, beliefs, attitudes, expectations and, as in behavioural therapy, change how people act. It is 'present-centred' and directs the individual to identify the current issues that are causing them distress, with the support of a trained psychological practitioner. Individuals talk about the specific problems in a structured manner with their therapist and may be given homework in the form of activities to complete before their next session. CBT is characterised as structured, goal-oriented and time-limited (Beck 1997).

## Complementary or alternative therapies

While we cannot provide an exhaustive description of all interventions that could be used to treat anxiety there are a mix of alternative therapies that patients may seek. For example self-help manuals, with limited therapist involvement may assist patients in gaining understanding or insight into their emotional problems, can be used to treat anxiety disorders or severe symptoms (Van Boeijen 2005). Other therapies such as exercise training, which may act as a buffer for stress or trigger the release of monoamine neurotransmitters, and relaxation therapy, which teaches individuals to recognise the symptoms of anxiety and respond to them with a technique that reduces arousal, have also been used to treat anxiety (Jorm 2004).

## How the intervention might work

Pharmaceutical interventions work by altering the level of certain neurotransmitters in the brain, while psychological interventions aim to alter maladaptive behaviour and cognitions in order to improve emotional functioning. There are multiple mechanisms through which treatments in the complementary and alternative category could work. Additionally, a placebo effect is also possible, whereby participants receiving standard care, or those waiting to receive an intervention, experience a reduction in anxiety symptoms that is not directly related to the action of the intervention treatment.

## Why it is important to do this review

Anxiety after stroke has received substantially less attention, both clinically and in research, than other psychological outcomes. Systematic reviews have already been carried out to assess the effectiveness of interventions used to treat depression and emotionalism when they occur after stroke (Hackett 2008; Hackett 2010). Currently there are no equivalent published systematic reviews of interventions used to treat anxiety after stroke, thus highlighting a gap in the literature and knowledge base. Studies in stroke (Shimoda 1998) and non-stroke populations (Wittchen 2003) have shown that anxiety increases the risk and severity of depression. Hence, early treatment of anxiety could reduce the risk of subsequent depression and its associated adverse consequences. Clinical guidelines have been established for treating anxiety, but their effectiveness in stroke populations remains unknown. We chose to evaluate any intervention whose primary aim was to treat anxiety after stroke as evidence suggests diversity among the preference of patients (Hyde 2005; Riedel-Heller 2005). However, we did expect that the majority of the trials retrieved would be pharmaceutical or psychologically-based interventions.

## OBJECTIVES

1. The primary aim of this review was to assess the effectiveness of pharmaceutical, psychological, complementary or alternative therapy interventions in treating anxiety disorders or symptoms in stroke patients.
2. The secondary aim was to identify whether any of these interventions for anxiety had an effect on quality of life, disability, depression, social participation, caregiver burden or risk of death.

## METHODS

## Criteria for considering studies for this review

### Types of studies

Randomised controlled trials (RCTs) where the primary aim of the intervention was to treat anxiety in people with a clinical diagnosis of stroke (Hatano 1976) were eligible for inclusion in this review. There was no restriction on the basis of language or study location. We expected eligible trials to compare the effect of an intervention plus usual care against placebo, a different intervention, or different doses or frequency of interventions. Trials had to have a placebo or standard care control arm otherwise they were not eligible for inclusion.

### Types of participants

All stroke patients enrolled into a RCT had to have either a clinical diagnosis of an anxiety disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III (APA 1980), DSM-III-R (APA 1987), DSM-IV (APA 1994), DSM-IV-TR (APA 2000)) or similar diagnostic criteria. Stroke patients in RCTs deemed to have significant levels of anxiety symptoms as established by a pre-determined researcher's defined cut-off score on an anxiety screening tool were also eligible. There were no restrictions on age distribution or gender. Studies with mixed populations of Ischaemic or haemorrhagic stroke were eligible but we excluded studies assessing treatment effect in an exclusively subarachnoid haemorrhage patient population as the characteristics, treatment, and management of these patients are substantially different to other stroke patients. Studies treating stroke patients for other conditions such as depression, cognitive impairment or physical disability were also ineligible, unless it could be determined that all patients had co-morbid anxiety upon enrolment into the trial and treatment of the anxiety was one of the main objectives of the trial.

### Types of interventions

We evaluated RCTs of pharmaceutical interventions administered to stroke patients compared with placebo or standard care. The purpose of administering the drug had to be to treat anxiety. We excluded trials where drugs were administered for other purposes, such as neuro-protection. We included psychological interventions compared with placebo or standard care, which aimed to treat anxiety. We expected that these types of interventions would have a clearly defined psychological component, be structured, delivered and supervised by trained staff, and be time-limited. We excluded interventions whose purpose was simply to provide information or educate patients. We did not include trials such as occupational therapy or stroke support co-ordinator visitation unless they had a definitive psychological component aimed at treating anxiety.

## Types of outcome measures

### Primary outcomes

The primary outcomes of interest were:

1. the proportion of stroke patients without a clinical diagnosis of an anxiety disorder according to the DSM (APA 1994) or another standard diagnostic classification at the end of scheduled follow-up;
2. the proportion of stroke patients scoring outside the anxiety symptom range (as defined by study author); or the change score from baseline on an anxiety rating scale or via self-report at the end of scheduled follow-up.

### Secondary outcomes

1. Co-morbid depression, as diagnosed by DSM or determined by a depression rating scale such as the Beck Depression Inventory (BDI) (Beck 1961), the Hamilton Depression scale (HAM-D) (Hamilton 1960) or the Montgomery-Asberg Depression Rating Scale (Montgomery 1979).
2. Quality of life as measured on scales such as the 36-item short form questionnaire (SF-36) (Ware 1993).
3. Social activities as measured on scales such as the Frenchay Activities Index (Wade 1985).
4. Activities of daily living as measured on scales such as the Barthel Index (Mahoney 1965).
5. Principal caregiver burden as measured by scales such as the Zarit Caregiver Burden Interview (Zarit 1980).
6. Any adverse consequence as a result of treatment for anxiety such as drug tolerance, co-dependence on counsellor or death. We also recorded loss to follow-up rates in different arms of trials as a possible indicator of treatment acceptability.

## Search methods for identification of studies

See the 'Specialized register' section in the [Cochrane Stroke Group](#) module.

### Electronic searches

We searched the trials register of the Cochrane Stroke Group (last searched October 2010). In addition, we also searched the following bibliographic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2010 Issue 4, searched October 2010);
2. MEDLINE (1950 to October 2010) (Appendix 1);
3. EMBASE (1947 to October 2010) (Appendix 2);
4. PsycINFO (1806 to October 2010) (Appendix 3);

5. Allied and Complementary Medicine database (AMED) (1985 to October 2010);
6. Cumulative Index to Nursing and Allied Health (CINAHL) (1982 to October 2010);
7. Proquest Digital Dissertations which houses theses from North American and select European universities (1861 to October 2010).

### Searching other resources

In an effort to identify further published, unpublished and ongoing trials we:

1. searched the following ongoing trials registers: ClinicalTrials.gov (<http://www.clinicaltrials.gov/>), Stroke Trials Registry ([www.strokecenter.org/trials/](http://www.strokecenter.org/trials/)), Current Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com)) (February 2011);
2. searched the conference proceedings from the UK Stroke Forum (2006 to 2010), European Stroke Conference (2001 to 2010), and the International Stroke Conference (2007 to 2010) not already searched by the Cochrane Stroke Group Trials Search Co-ordinator;
3. searched PsycBITE (Psychological Database for Brain Impairment Treatment Efficacy) (<http://www.psycbite.com/>), accessed February 2011;
4. used Science Citation Index Cited Reference search for forward tracking of relevant articles;
5. scanned the bibliographies of identified trials;
6. contacted experts known to our research group and researchers with expertise in psychological disorder research, identified by scanning authors of relevant publications;
7. contacted the Association of British Pharmaceutical Industry, which includes the large majority of research-based pharmaceutical companies, to request information about any relevant unpublished trials. We did not receive any responses. However, there is compulsory registration of trials on public domain sites such as [Clinicaltrials.gov](http://Clinicaltrials.gov) and [controlled-trials.com](http://controlled-trials.com), therefore, making it unlikely that additional trials would be found.

We searched for relevant trials in all languages and arranged translation of trial reports published in languages other than English.

## Data collection and analysis

### Selection of studies

Two review authors (ACB and PK) independently screened all reports yielded from the searches of electronic databases, and excluded citations that were clearly irrelevant based on title and abstract. We retrieved the full text of the remaining articles and reviewed them for inclusion based on the eligibility criteria for the review. If a consensus could not be reached, we had planned to



consult a third review author (DG) for adjudication. However, this was not necessary.

### Data extraction and management

Two review authors (ACB and JM) independently extracted data onto a paper extraction form where key information from studies was recorded. If information was missing, one review author (ACB) attempted to contact the study authors, either by telephone or email, to request the missing data. After the two authors reconciled the data extraction, it was entered into Review Manager 5 (RevMan 2011). We recorded the following core data elements such as study details, methods, information about participants and outcomes for analysis.

### Assessment of risk of bias in included studies

We assessed study bias in accordance with The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008). This instrument has six domains whereby different types of potential biases can be evaluated. The domains are sequence generation, allocation concealment, blinding (of participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting and other unspecified types of bias (e.g. conflict of interest). We identified the respective biases from each study and displayed them in a tabular format. We summarised the risks qualitatively and attempted to describe their impact on the research findings.

### Measures of treatment effect

A narrative description of all studies was conducted. Both included trials measured anxiety using the Hamilton Anxiety Scale (HAM-A) (Hamilton 1959). The Hamilton Anxiety Scale is a rating scale developed to quantify the severity of anxiety symptomatology, and is often used in psychotropic drug evaluation. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a five-point scale, ranging from zero (not present) to four (severe). Total scores on the HAM-A range from zero to 56. A score of 14 or more has been suggested to indicate clinically significant anxiety.

### Unit of analysis issues

In the event of outcomes being repeatedly observed in participants (e.g. follow-up at four and six weeks), we reported the measurement taken at the longest time point post intervention from each study.

### Dealing with missing data

We planned to contact study authors to obtain information about missing data and, if unobtainable, conduct a 'what if' sensitivity analysis exploring the impact the missing data could have on the final outcome.

### Assessment of heterogeneity

The intent was to measure heterogeneity with the  $I^2$  statistic. If higher than 50% (a level considered to be a moderate to substantial level), we would have reported the random-effects method to measure treatment effect. The random-effects method assumes that different studies are estimating different but related intervention effects and so provides a more conservative intervention effect estimate and wider confidence intervals (DerSimonian 1986).

### Assessment of reporting biases

We planned to construct a funnel plot estimate to assess the potential influence of reporting bias in the event of more than 10 studies being included in the systematic review.

### Data synthesis

Two review authors (ACB and JM) independently extracted data from included studies. One review author (ACB) entered data into RevMan (RevMan 2011) and JM cross-checked the data entry. The review authors resolved disagreements through reference to the original study report.

### Subgroup analysis and investigation of heterogeneity

Several factors could impact heterogeneity of studies and effect size. We initially planned to undertake subgroup analyses on certain clinically relevant factors, such as specific type of anxiety disorder (e.g. GAD or social phobia), length of time treatment was administered, or length of time since stroke at entry into the trial.

### Sensitivity analysis

To test the robustness of findings and examine the degree to which they influenced the effect size, we planned to analyse data and include studies whereby allocation concealment, double blinding, and fidelity to administered intervention were executed to the highest standard.

## RESULTS

### Description of studies

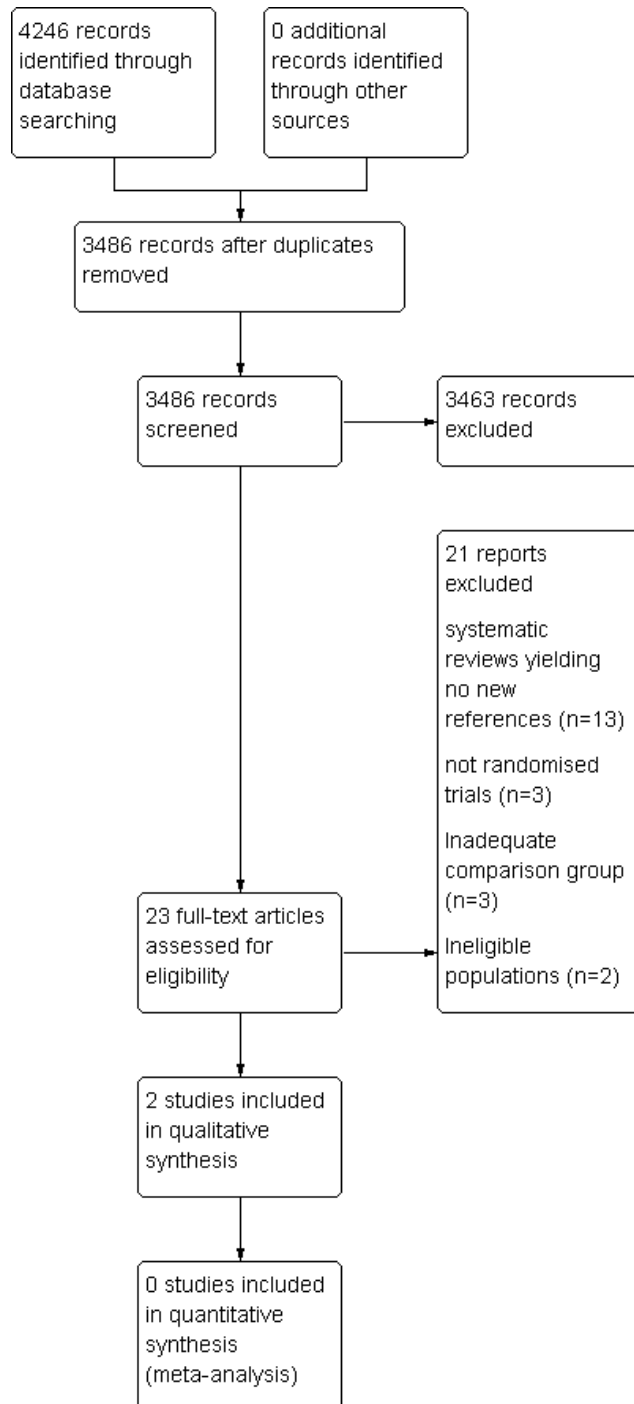
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

We did not identify any trials that compared any intervention with a placebo control. See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

### **Results of the search**

The search yielded a total of 3486 unique titles ([Figure 1](#)). ACB and PK carried out dual screening of all titles and abstracts and retrieved 10 papers for full text review. Additionally, the search yielded 13 systematic reviews that ACB reviewed for references. However, no new references were found using this method. ACB and JM conducted dual data extraction, and determined that two studies met the inclusion criteria for this review.

**Figure 1. Search flow diagram**



### Included studies

Two trials with a total of 175 randomised participants met our inclusion criteria (Wang 2005; Zhang 2005).

Wang 2005 evaluated the effectiveness of the selective serotonin reuptake inhibitor (SSRI) paroxetine, and combination paroxetine and psychotherapy. Eighty-one first-ever stroke patients who met the Chinese Classification and Diagnostic Criteria of Mental Disorders (CCMD-3) criteria were randomised to one of the three groups. The first group (27 patients) received 20 mg of paroxetine per day, while the second group (27 patients) received the same amount of paroxetine per day along with psychiatrist administered supportive psychotherapy for 30 to 60 minutes once per week. A parallel control group with 27 patients received routine treatment only. The study authors did not specify the length of time the participants were post-stroke at time of recruitment. Patients who were in a coma, aphasic, had severe cognitive dysfunction, other serious diseases or those who had been prescribed depression or antipsychotic medications in the three months prior to the onset of the trial were excluded. The interventions were carried out for six weeks and the HAM-A and the HAM-D scales were used to assess the severity of anxiety and depression symptoms at baseline and at the two, four and six week time points during the treatment. Scores on the Barthel Index measuring activities of daily living were also assessed at all time points. Mean ages of participants were as follows: 62.4 years drug only group, 64.0 years in the drug plus psychotherapy group, and 63.2 years in the standard care group. Zhang 2005 examined the effect of the anxiolytic drug buspirone hydrochloride against standard care. Ninety-four stroke patients with co-morbid anxiety and depression according to the CCMD-3 were recruited into the trial. Individuals with unstable conditions were deemed ineligible; however, no description of unstable conditions was provided. Buspirone was administered for four weeks to those in the intervention arm of the study. It was provided at 20 to 30 mg per dose during the first week, and then at 40 to 60 mg per dose during the second week. No information was provided about the amount administered during the third or fourth week. Anxiety and depression were measured using the HAM-A and the HAM-D scales at the baseline, and at two and four weeks during the intervention. The mean age of participants was 57.8 years for the intervention group, and 59.2 years for the control group. No other secondary outcome of interest was reported.

### Excluded studies

We excluded eight trials in total from the review. Three studies (Liu 2004; Ye 2006; Wu 2008) had no adequate control group (i.e. no placebo or standard care only group). In four studies anxiety levels of the participants were assessed but they did not necessarily meet

a pre-defined threshold definition so we could not establish that all participants had anxiety upon entry into the study (Morrison 1998; Mok 2004; Li 2005; Rorsman 2006). In addition, Morrison 1998, Kimura 2003, and Li 2005 were not randomised control trials. Morrison 1998 was a quasi experimental cohort study design using retrospective controls, and Li 2005 study participants acted as their own controls. The criteria for entry into Kimura 2003 was depression and a subset analysis on cases with co-morbid depression and GAD was conducted.

### Risk of bias in included studies

#### Allocation

Wang et al stated they used simple random sampling, and Zhang et al indicated they used a random number list for participants who met the inclusion criteria (Wang 2005; Zhang 2005). However, the randomisation process was not described in either study, hence the integrity of the sequence generation and allocation concealment were unclear.

#### Blinding

Neither study provided information about blinding (Wang 2005; Zhang 2005). As there was no placebo control group, blinding would likely only be possible for independent outcome assessors.

#### Incomplete outcome data

One study (Wang 2005) recruited 81 participants with none lost to follow-up. There was no indication that participants did not adhere to treatment protocol in this study. The other study (Zhang 2005) reported outcomes for participants who remained until completion of the study. Hence, it is classified as 'available case analysis'.

#### Selective reporting

There was no evidence of selective outcome reporting in any of the trials. All outcomes measured and reported in the methods of these studies at the onset of the trial were reported at all time points. However, we did not obtain the research protocols so we do not know if other outcomes were measured but not reported.

#### Effects of interventions

In the absence of any placebo-control group and because of generally poor description of the study processes we did not perform

a meta-analysis. The effectiveness of the interventions compared with standard care are described.

Wang et al found that both paroxetine, and paroxetine plus psychotherapy reduced the severity of anxiety symptoms as measured by the HAM-A when compared with standard care (Wang 2005). The mean HAM-A anxiety scores at baseline in the drug only, drug plus psychotherapy, and standard care groups were  $14.0 \pm$  (standard deviation (SD) = 2.8), 13.9 (SD = 2.9), and 13.8 (SD = 2.8) respectively. At six weeks the mean anxiety scores were significantly lower in the two intervention groups relative to the controls 5.4 (SD = 1.7), 3.8 (SD = 1.8) in the drug only, and drug plus psychotherapy groups, but remained at 12.8 (SD = 1.9) in the control group. Relative to the standard care group, this represents a 58% and 71% lower mean anxiety score in the paroxetine, and paroxetine plus psychotherapy groups respectively. These differences were statistically significant ( $P < 0.01$ ). A similar trend was observed for mean depression scores as measured by the HAM-D. The possible range on the HAM-D is zero to 54, with higher scores indicative of more severe symptoms. Mean depression severity scores were 18.2 (SD = 1.4), 18.8 (SD = 3.1), and 18.0 (SD = 1.3) at baseline in the paroxetine, paroxetine plus psychotherapy, and standard care groups respectively. While no change was observed in the control group after six weeks (mean 17.5, SD = 1.1), both the drug only and drug plus psychotherapy groups had significantly fewer depression symptoms (mean 10.1, SD = 1.1, and mean 8.9, SD = 1.2), respectively. This was also the only trial that reported changes in functional status as measured by the Barthel Index of activities of daily living (ADL). They found that ADL improved significantly in all three groups of patients but the greatest improvement was observed in the drug plus psychotherapy group, followed by the drug only group, with the standard care controls having the least amount of improvement.

Zhang et al found that buspirone hydrochloride was effective in reducing anxiety symptoms when compared with standard care (Zhang 2005). Four weeks after trial initiation the mean anxiety score on the HAM-A decreased from 22.7 (SD = 5.2) to 6.5 (SD = 3.1) in the intervention group. This was a significantly larger decrease than seen in the standard care group ( $P < 0.01$ ) where the mean anxiety score decreased from 22.5 (SD = 4.3) to 12.6 (SD = 3.4) after four weeks. The mean in the intervention group was 50% lower than those receiving standard care only. Buspirone was also effective in significantly reducing depression symptoms as measured on the HAM-D in the intervention group compared with the controls. The mean depression score in the intervention group decreased from 24.6 (SD = 4.7) to 8.3 (SD = 2.8) and from 23.4 (SD = 5.3) to 13.4 (SD = 2.7) in the standard care group.

The HAM-A scores range from zero to 54 with a score of more than 17 indicative of mild to moderate anxiety symptoms. On this basis the reduction in anxiety scores in the intervention groups in both trials appear to be meaningful. However, the authors did not report their findings in terms of proportion no longer anxious so the clinical significance of the effect is uncertain.

### Adverse events and loss to follow-up

No participants were lost to follow-up in the Wang et al trial (Wang 2005). However, in both the intervention and control groups 23% of participants were lost in the Zhang et al trial (Zhang 2005). Reasons given for drop out in the intervention group were unsatisfactory treatment effect, drug side effects, and subsequent prescription of benzodiazepines. Recurrent stroke, having benzodiazepines prescribed, and withdrawal were reasons given for loss to follow-up in the control group.

Over 50% of participants receiving paroxetine in the Wang et al study reported nausea or dizziness (Wang 2005), while 14% of those receiving buspirone in the Zhang et al study reported either nausea, dizziness or heart palpitations (Zhang 2005).

## DISCUSSION

### Summary of main results

To our knowledge, this is the first systematic review of interventions to treat anxiety after stroke. We found two published trials and no ongoing trials. Of the two published trials, anxiety symptom severity as measured by the Hamilton Anxiety Scale was the outcome of interest. Neither study evaluated clinical anxiety disorders or had a placebo control group. The results suggest that both paroxetine and buspirone are effective therapies for treating anxiety after stroke. However, in the absence of a placebo control arm, the true level of effectiveness is uncertain. Combining paroxetine and psychotherapy did not confer any significant additional benefit for stroke patients. Paroxetine appears to be well tolerated as there were no drop-outs among the patients but a large proportion experienced symptoms of nausea or dizziness. Buspirone was also effective in reducing anxiety, but there was substantial loss to follow-up and some adverse events were reported. The loss to follow-up in the buspirone trial is unusual as there was an equally high level of drop out in the control group.

### Overall completeness and applicability of evidence

This review was deliberately broad as we suspected the literature on interventions used to treat anxiety after stroke was not as established as some of the other post-stroke psychological conditions. We attempted to collate comprehensive evidence relevant to the review question. Very little information was provided about the populations from which the participants were selected, hence the findings of this review may not even be generalisable to the stroke population from which they were drawn let alone stroke populations in other locales. Another concern was the inclusion criteria for both studies required participants to have co-morbid

anxiety and depression according to the CCMD-3. This would result in stroke patients with only anxiety being deemed ineligible for inclusion into the trial. As a result there is no evidence as to whether any of the interventions described would be effective for stroke patients who only had anxiety and not depression. It should be noted that while the HAM-A is widely used in pharmaceutical studies of anxiety it is not appropriate as a diagnostic or screening instrument. The HAM-A focuses primarily on the phobic and autonomic arousal symptoms of anxiety, and gives little weight to the psychic symptoms. Given the physical consequences of stroke, it would be misleading to attribute all physical symptoms solely to anxiety after stroke.

### Quality of the evidence

Clear conclusions about the evidence cannot be drawn as many of the quality indices were not adequately described, and study sample size was small in both of the included trials. No study provided information on the length of time that had passed between stroke and participant enrolment into the trial and no information was provided about the setting from which participants were recruited (e.g. hospital, or community based), which could influence prevalence of anxiety as hospital patients tend to have higher levels of mood disturbance. Another issue is that neither study described what was involved in the routine or standard care groups which were used as the control comparison. Lastly, all studies inadequately reported their methodological indices such as allocation concealment or blinding of participants and outcome assessors.

### Potential biases in the review process

To the extent possible, there was minimal bias in the review process. We undertook an extensive literature search guided by the Cochrane Stroke Group, and contacted key researchers in the field to obtain information about studies with a focus on post-stroke anxiety. Additionally, we did not limit findings to English only papers. Two review authors independently decided whether studies should be included and data were extracted independently by two review authors.

### Agreements and disagreements with other studies or reviews

To our knowledge there are no other systematic reviews of interventions used to treat anxiety after stroke.

## AUTHORS' CONCLUSIONS

### Implications for practice

Currently there is insufficient evidence to guide practice in treating anxiety after stroke. The pharmaceutical therapies evaluated indicate that medication may be an effective approach for reducing anxiety symptoms in stroke patients with co-morbid anxiety and depression when compared with standard care. The clinical significance of this decrease is unclear as the authors did not provide any information about the proportion of study participants no longer meeting the anxiety criteria. However, research has indicated that a reduction of more than 50% on the Hamilton Anxiety Scale is indicative of obvious improvement in the level of anxiety (Ye 2006).

### Implications for research

Given the high prevalence of anxiety after stroke, placebo controlled trials are needed to identify effective treatments for this condition, as it can have a negative impact on other aspects of life. Future research evaluating interventions to treat post-stroke anxiety should assess outcomes such as quality of life and caregiver burden as the trials in this review provided no information to determine any impact of treatment on these outcomes. It will also be useful for trials to investigate the effectiveness of psychological interventions as none were found in this systematic review, and for them to recruit patients with anxiety only as well as those with co-morbid anxiety and depression.

## ACKNOWLEDGEMENTS

We are very grateful to Hazel Fraser who facilitated the entire review process, Brenda Thomas of the Cochrane Stroke Group who helped develop the search strategies, searched the Cochrane Stroke Group Trials Register and the Cochrane Central Register of Controlled Trials, and Mr Mark Clowes of University of Leeds who assisted with the various database searches. Additionally, we are indebted to Professor Mei-Chuin Tseng whose translation of several articles made the review possible. Lastly, many thanks to the peer reviewers for their helpful comments on the review (Professor Peter Langhorne, Dr Maree Hackett, Dr Gillian Mead, Ms Ashma Krishan, and Mrs Brenda Thomas).

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Wang 2005

Methods	RCT
Participants	Location: China 81 CT/MRI confirmed first ever stroke according to CCMD-3 criteria with co-morbid anxiety and depression Group 1: 52% male, mean age 62.4 years (SD 6.1) Group 2: 52% male, mean age 64.0 years (SD 5.3) Group 3: 52% male, mean age 63.2 years (SD 5.7)
Interventions	Intervention group 1: 27 participants, paroxetine 20 mg daily + routine treatment Intervention group 2: 27 participants, paroxetine 20 mg daily + routine treatment + psychiatrist administered individual supportive psychotherapy (30 to 60 minutes per week) Group 3: 27 participants, control group routine treatment only Duration: 6 weeks
Outcomes	Anxiety (HAM-A), depression (HAM-D), BI at 2, 4 and 6 weeks Loss to follow-up: none Adverse events: 26 1. Group 1: (14 total): minor nausea or stomach distension (9), dizziness (5) 2. Group 2: (12 total): minor nausea and vomiting (10), dizziness (2) 3. Group 3: none reported Other outcomes: neurological impairment (SSS), activities of daily living (BI)
Notes	Exclusions: coma, aphasia, severe cognitive dysfunction, other serious diseases, depression or antipsychotic medications within 3 months, allergic to paroxetine, or bipolar disorder

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random number list (details not provided)
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) Anxiety	Unclear risk	Unknown
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not applicable; data available from all participants recruited to study

**Wang 2005** (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes measured at the onset of trial reported at all time points
Other bias	Unclear risk	Unknown

**Zhang 2005**

Methods	RCT
Participants	Location: China 94 patients (47 each in control and intervention group) with clinical diagnosis of stroke according to CCMD-3 criteria and affective disorders (72 included in final analysis) Intervention group: 64% male, 57.8 years (SD 6.4) Control group: 61% male, 59.2 years (SD 5.8)
Interventions	Intervention group: 36 participants, buspirone hydrochloride 20 to 30 mg daily in first week, 40 to 60 mg in second week + routine care Control group: 36 participants, routine care (no description of routine care) Duration: 4 weeks
Outcomes	Anxiety (HAM-A) and depression (HAM-D) at 2 and 4 weeks Loss to follow-up: 22 (11 in each group) 1. Intervention group: 7 withdrew before treatment, 1 unsatisfactory treatment effects, 2 due to adverse effects, 1 prescribed benzodiazepines 2. Control group: 6 withdrew before treatment, 1 recurrent stroke, 4 prescribed benzodiazepines Adverse effects: 5 1. Intervention group: 3 dizziness and nausea, 2 palpitations Other outcomes: American Heart Stroke Outcome Classification
Notes	Exclusion: patients with unstable conditions

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Anxiety	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided

**Zhang 2005** (Continued)

Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	No information provided

BI: Barthel Index

CCMD-3: Chinese Classification of Mental Disorders Version 3

CT: computed tomography

HAM-A: Hamilton Anxiety Scale

HAM-D: Hamilton Depression Rating Scale

MRI: magnetic resonance imaging

RCT: randomised controlled trial

SD: standard deviation

SSS: Scandinavian Stroke Scale

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Kimura 2003	Design: cohort design Allocation: unclear Blinding: double blind Participants: post-stroke with clinical diagnosis of moderate to severe depression. GAD only patients excluded. This study carried out secondary analysis on a subset (27/106) participants who had co-morbid GAD Intervention: daily nortriptyline 20 to 100 mg for 6 weeks. Dose escalated to 100 mg over duration of study; placebo control
Li 2005	Design: self-controlled study Allocation: not applicable Blinding: unclear Participants: post-stroke (all had anxiety levels measured, but did not necessarily meet any criteria to be defined as anxious) Interventions: early functional training which included component of supportive treatment without anti-anxiety or antidepressant prescriptions. No placebo or standard care comparison
Liu 2004	Design: RCT Allocation: number list, taking into account age, gender, and patient condition Blinding: double blinded Participants: post-stroke with anxiety (HAM-A $\geq$ 14) Intervention: group 1 received 0.2 mg alprazolam every 8 hours + fluoxetine 20 mg once daily; group 2: alprazolam every 8 hours. No placebo or standard care comparison
Mok 2004	Design: RCT Allocation: random drawing of lots Blinding: none, 1 researcher collected all data

(Continued)

	Participants: post-stroke (anxiety assessed using Chinese State-Trait Anxiety Inventory, in all participants, but did not necessarily meet criteria to be defined as anxious) Intervention: slow stroke back massage
Morrison 1998	Design: quasi experimental cohort, with retrospective controls Allocation: not applicable Blinding: not applicable Participants: post-stroke (level of anxiety assessed in all participants, but not necessarily meeting criteria for anxiety) Intervention: self-help workbook aimed at enhancing non-avoidant coping and increasing personal control over recovery
Rorsman 2006	Design: RCT Allocation: yes, opaque randomised envelopes, numbered consecutively produced centrally by a computer Blinding: yes, study co-ordinator and evaluators not granted to access on allocation Participants: post-stroke only (all had anxiety levels measured, but did not necessarily meet any criteria to be defined as anxious) Interventions: group 1: electroacupuncture; group 2: transcutaneous electrical nerve stimulation
Wu 2008	Design: RCT Allocation: process unclear Blinding: not indicated Participants: post-stroke anxiety neurosis (ICD-10) Interventions: group 1 received alprazolam, group 2 received acupuncture. No placebo or standard care comparison
Ye 2006	Design: RCT Allocation: unclear (not described) Blinding: double blind (not described) Participants: 90 stroke patients with co-morbid anxiety and depression defined as (> 14 on HAM-A and > 21 on HAM-D) Interventions: group 1 received paroxetine, group 2 received imipramine, control group received standard care and rehabilitative training. No placebo or standard care only comparison

GAD: generalised anxiety disorder

HAM-A: Hamilton Anxiety Scale

HAM-D: Hamilton Depression Rating Scale

ICD: International Classification of Diseases

RCT: randomised controlled trial

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix I. MEDLINE search strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vas\$ or cerebral vas\$ or cva\$ or apoplex\$ or SAH).tw.
3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
7. brain injuries/ or brain injury, chronic/
8. or/1-7
9. anxiety/
10. anxiety disorders/ or agoraphobia/ or obsessive-compulsive disorder/ or panic disorder/ or phobic disorders/ or exp stress disorders, traumatic/
11. exp Anti-Anxiety Agents/
12. (anxiety or anxieties or anxious or agoraphobi\$ or phobi\$ or panic disorder\$ or panic attack\$ or (obsess\$ adj3 compuls\$) or post? traumatic stress\$ or PTSD).tw.
13. (feel\$ adj5 (apprehens\$ or dread or disaster\$ or fear\$ or worry or worried or terror)).tw.
14. manifest anxiety scale/
15. or/9-14
16. 8 and 15
17. Randomized Controlled Trials as Topic/
18. random allocation/
19. Controlled Clinical Trials as Topic/
20. control groups/
21. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
22. double-blind method/
23. single-blind method/
24. Placebos/
25. placebo effect/
26. cross-over studies/
27. Multicenter Studies as Topic/
28. Therapies, Investigational/
29. Drug Evaluation/
30. Research Design/
31. Program Evaluation/
32. evaluation studies as topic/
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.

36. multicenter study.pt.
37. (evaluation studies or comparative study).pt.
38. random\$.tw.
39. (controlled adj5 (trial\$ or stud\$)).tw.
40. (clinical\$ adj5 trial\$).tw.
41. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
42. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
43. ((multicenter or multicentre or therapeutic) adj5 (trial\$ or stud\$)).tw.
44. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
45. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
46. (coin adj5 (flip or flipped or toss\$)).tw.
47. (cross-over or cross over or crossover).tw.
48. placebo\$.tw.
49. sham.tw.
50. (assign\$ or alternate or allocat\$ or counterbalance\$ or multiple baseline).tw.
51. controls.tw.
52. (treatment\$ adj6 order).tw.
53. or/17-52
54. 16 and 53
55. limit 54 to humans

## Appendix 2. EMBASE search strategy

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke/ or stroke patient/ or stroke unit/
2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.
3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or oclus\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
5. paralysis/ or hemiparesis/ or hemiplegia/ or paresis/
6. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
7. brain injury/
8. or/1-7
9. anxiety/
10. exp anxiety disorder/
11. exp anxiolytic agent/
12. (anxiety or anxieties or anxious or agoraphobi\$ or phobi\$ or panic disorder\$ or panic attack\$ or (obsess\$ adj3 compuls\$) or post? traumatic stress\$ or PTSD).tw.
13. (feel\$ adj5 (apprehens\$ or dread or disaster\$ or fear\$ or worry or worried or terror)).tw.
14. beck anxiety inventory/ or hamilton anxiety scale/ or "hospital anxiety and depression scale"/ or self-rating anxiety scale/ or state trait anxiety inventory/
15. or/9-14
16. Randomized Controlled Trial/
17. Randomization/
18. Controlled Study/
19. control group/
20. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
21. Crossover Procedure/
22. Double Blind Procedure/
23. Single Blind Procedure/ or triple blind procedure/

24. placebo/
25. Multicenter Study/
26. experimental design/ or experimental study/ or quasi experimental study/
27. experimental therapy/
28. drug comparison/ or drug dose comparison/
29. evaluation/ or "evaluation and follow-up"/ or evaluation research/ or clinical evaluation/
30. methodology/
31. "types of study"/
32. research subject/
33. Comparative Study/
34. random\$.tw.
35. (controlled adj5 (trial\$ or stud\$)).tw.
36. (clinical\$ adj5 trial\$).tw.
37. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
38. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
39. ((multicenter or multicentre or therapeutic) adj5 (trial\$ or stud\$)).tw.
40. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
41. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
42. (coin adj5 (flip or flipped or toss\$)).tw.
43. (cross-over or cross over or crossover).tw.
44. placebo\$.tw.
45. sham.tw.
46. (assign\$ or alternate or allocat\$ or counterbalance\$ or multiple baseline).tw.
47. controls.tw.
48. (treatment\$ adj6 order).tw.
49. or/16-48
50. 8 and 15 and 49
51. limit 50 to human

### Appendix 3. PsycINFO search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or exp cerebral ischemia/ or cerebral small vessel disease/ or cerebrovascular accidents/ or subarachnoid hemorrhage/
2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.
3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
5. hemiparesis/ or hemiplegia/
6. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
7. brain injur\$.tw.
8. or/1-7
9. exp anxiety/
10. exp anxiety disorders/ or panic/ or panic attack/ or fear/
11. anxiety management/
12. state trait anxiety inventory/ or taylor manifest anxiety scale/
13. (anxiety or anxieties or anxious or agoraphobi\$ or phobi\$ or panic disorder\$ or panic attack\$ or (obsess\$ adj3 compuls\$) or post? traumatic stress\$ or PTSD).tw.
14. (feel\$ adj5 (apprehens\$ or dread or disaster\$ or fear\$ or worry or worried or terror)).tw.
15. or/9-14
16. 8 and 15
17. random sampling/
18. experiment controls/



19. placebo/
20. (empirical study or treatment outcome clinical trial).md.
21. clinical trials/ or Treatment Effectiveness Evaluation/
22. random\$.tw.
23. (controlled adj5 (trial\$ or stud\$)).tw.
24. (clinical\$ adj5 trial\$).tw.
25. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
26. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
27. ((multicenter or multicentre or therapeutic) adj5 (trial\$ or stud\$)).tw.
28. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
29. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
30. (coin adj5 (flip or flipped or toss\$)).tw.
31. (cross-over or cross over or crossover).tw.
32. placebo\$.tw.
33. sham.tw.
34. (assign\$ or alternate or allocat\$ or counterbalance\$ or multiple baseline).tw.
35. controls.tw.
36. (treatment\$ adj6 order).tw.
37. or/17-36
38. 16 and 37

## HISTORY

Protocol first published: Issue 12, 2010

Review first published: Issue 12, 2011

## CONTRIBUTIONS OF AUTHORS

Campbell Burton is a PhD candidate in healthcare studies, Holmes is a senior lecturer in old age liaison psychiatry, Murray is a senior research fellow in cardiovascular care, Gillespie is a practising clinical psychologist, Lightbody is a research fellow in stroke, Watkins is a nursing professor in stroke care, and Knapp is a research psychologist.

Campbell Burton co-ordinated and led the review. All authors contributed to the drafting of the protocol. Campbell Burton and Knapp carried out independent screening of papers and formed consensus on studies for inclusion in the review. Murray and Campbell Burton independently extracted data. Campbell Burton conducted the data entry, analysis, and wrote the first draft of the review. All review authors contributed to the final draft.

## DECLARATIONS OF INTEREST

None known.

## **SOURCES OF SUPPORT**

### **Internal sources**

- University of Leeds, UK.

### **External sources**

- No sources of support supplied